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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,522	04/12/2006	Nafizal Hossain	06275-503US1	3659

26164 7590 12/14/2007

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EXAMINER	
O'DELL, DAVID K	
ART UNIT	**PAPER NUMBER**
1625	
MAIL DATE	**DELIVERY MODE**
12/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,522	HOSSAIN, NAFIZAL	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-18* is/are pending in the application.

4a) Of the above claim(s) *8,10 and 12-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10, 12-18 are pending in the current application.

2. This is a National Stage of PCT/SE2004/001476, filed October 14, 2004, which claims priority to Swedish Application Serial No. 0302755-4, filed October 17, 2003.

Response to Remarks Arguments

3. Applicant's arguments filed November 13, 2007 have been fully considered but they are not persuasive. The rejections under 35 U.S.C. 103 (a) are withdrawn in light of applicant's statement of common assignment. The rejection for solvate is withdrawn, it is noted that claim 7 also appears to contain solvate, which was unintentionally overlooked by the examiner. Rather than repeat another rejection and based upon applicant's willingness to delete this term, the examiner is not rejecting this claim for "solvate" and depends upon the applicant to remove this term. The rejections for scope of enablement are maintained as the directions for the preparation and use of the compounds commensurate in scope with the claims has not been provided. The number of examples provided by the specification are few and have been discussed previously (and are reproduced here again vide infra). It would appear that the applicant is arguing that essentially any molecule, even molecules of unknown structure, can be made without undue experimentation. This is in fact not the situation in the chemical arts. As stated in a recent book on the subject:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and

synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work.....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) [preface].....even structurally simple compounds often turn out not to be so easy to make as initially thought. [pg. 2]..... As illustrated by the examples discussed below, a good retrosynthesis requires much synthetic experience, a broad knowledge of chemical reactivity, and the ability to rapidly recognize synthetically accessible substructures [pg. 3]..... As will be shown throughout this book, the outcome of organic reactions is highly dependent on all structural features of a given starting material, and unexpected products may readily be formed. [8].....Even the most experienced chemist will not be able to foresee all potential pitfalls of a synthesis, specially so if multifunctional, structurally complex intermediates must be prepared. The close proximity or conformational fixation of functional groups in a large molecule can alter their reactivity to such an extent that even

> simple chemical transformations can no longer be performed. Small structural variations of polyfunctional substrates might, therefore, bring about an unforeseeable change in reactivity [pg. 9]....." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface pg. 1-15.

The examiner (*vide infra* and in the previous action) serve to show the scope that is enabled by the specification, in terms of the compounds, and the teaching of the prior art. A recent ruling by the Federal circuit discusses enablement in the context of the automotive art, but there is little difference in the position of the court and the position of the examiner instant case, ATI v. BMW et. al. (Fed. Cir. 2007):

> "We also reject ATI's argument that because the specification enables one mode of practicing the invention, viz., mechanical side impact sensors, the enablement requirement is satisfied. We addressed and rejected a similar argument made in Liebel-Flarsheim Co. v. Medrad, Inc., 481 F.3d 1371 (Fed. Cir. 2007). In that case, the invention was a front-loading fluid injector system with a replaceable syringe capable of at 1373. We construed the asserted claims, as urged by the patentee, to include an injector with and without a pressure jacket. Although the specification clearly enabled an injector with a pressure jacket, we concluded that it did not enable an injector without such a jacket and that the claims were invalid for lack of enablement. at 1379. We stated that there "must be 'reasonable enablement of the scope of the range' which, in this case, includes both injector systems with and without a pressure jacket." withstanding high pressure for delivering a contrast agent to a patient. Id. Id. Id. at 1380 (internal citation omitted).
>
> Similarly, in this case, the claim construction of the relevant claim limitation resulted in the scope of the claims including both mechanical and electronic side impact sensors. Disclosure of only mechanical side impact sensors does not permit one skilled in the art to make and use the invention as broadly as it was claimed, which includes electronic side impact sensors. Electronic side impact sensors are not just another known species of a genus consisting of sensors, but are a distinctly different sensor compared with the well-enabled mechanical side impact sensor that is fully discussed in the specification. Thus, in order to fulfill the enablement requirement, the specification must enable the full scope of the claims that includes both electronic and mechanical side impact sensors, which the specification fails to do. We stated in Liebel: "The irony of this situation is that Liebel successfully pressed to have its claims include a jacketless system, but, having won that battle, it then had to show that such a claim was fully enabled, a challenge it could not meet." Id. at 1380. ATI sought to have the scope of the claims of the '253 patent include both mechanical and electronic side impact sensors. It succeeded, but then was unable to demonstrate that the claim was fully enabled. Claims must be enabled to correspond to their scope."

The very limited disclosure and the inordinate amount of experimentation required to practice the invention, clearly warrant the conclusion made by the examiner, which was supported by references testifying to the state of the art and its unpredictability. This action is made **FINAL**.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8, 10 of copending Application No. 10/579,545 in view of Xue et. al. U.S. Pre-Grant Publication 2006/0252751. The analysis applied in this action at 4 applies here. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Determination of the scope and content of the prior art

(MPEP 2141.01)

Xue et. al. teaches spiro[benzofuran-2,1'-cyclohexan]-4'-amines that are chemokine antagonists. 10/579,545 teach spiro[benzofuran-2,4'-piperidines bearing a 1-phenoxy-3-propan-2-ol substituent on the piperidinyl nitrogen atom. This relationship is illustrated graphically in Figure 1.

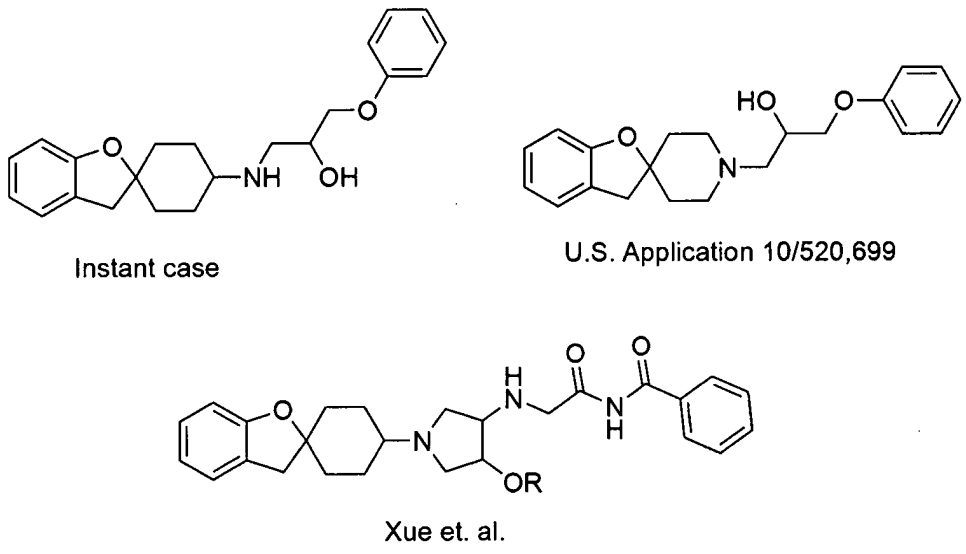
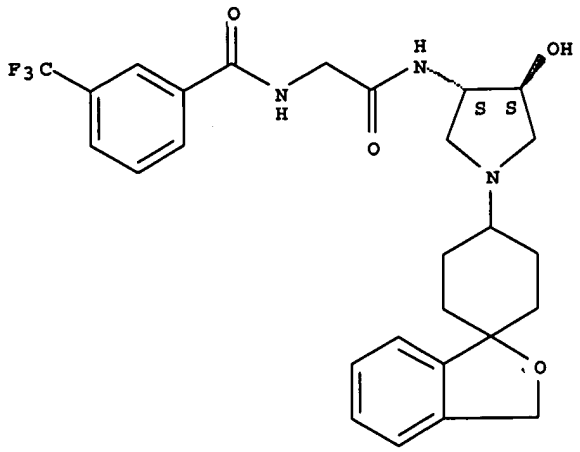


Figure 1. Structures of compounds that form the basis of the obviousness rejection as compared to the instant invention.

Some of the compounds disclosed by Xue are show below:

Registry #: 709018-09-7



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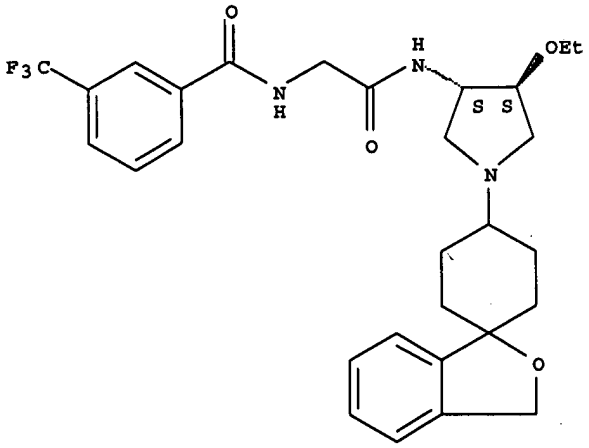


Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Hossain, Nafizal; Ivanova, Svetlana & Mensonides-Harsema, Marguerite do not expressly teach the compounds of the instant case, however the only difference between these compounds is the presence of a methylene group. By inserting a what is formally a methylene (CH_2 actually CH in the ring and H on N) into the compounds of Hossain, Nafizal; Ivanova, Svetlana & Mensonides-Harsema, Marguerite a spiro[benzofuran-2,1'-cyclohexan]-4'-amine is produced, which is a core

pharmacophore of chemokine antagonism. These relationships are illustrated graphically in Figure 2.

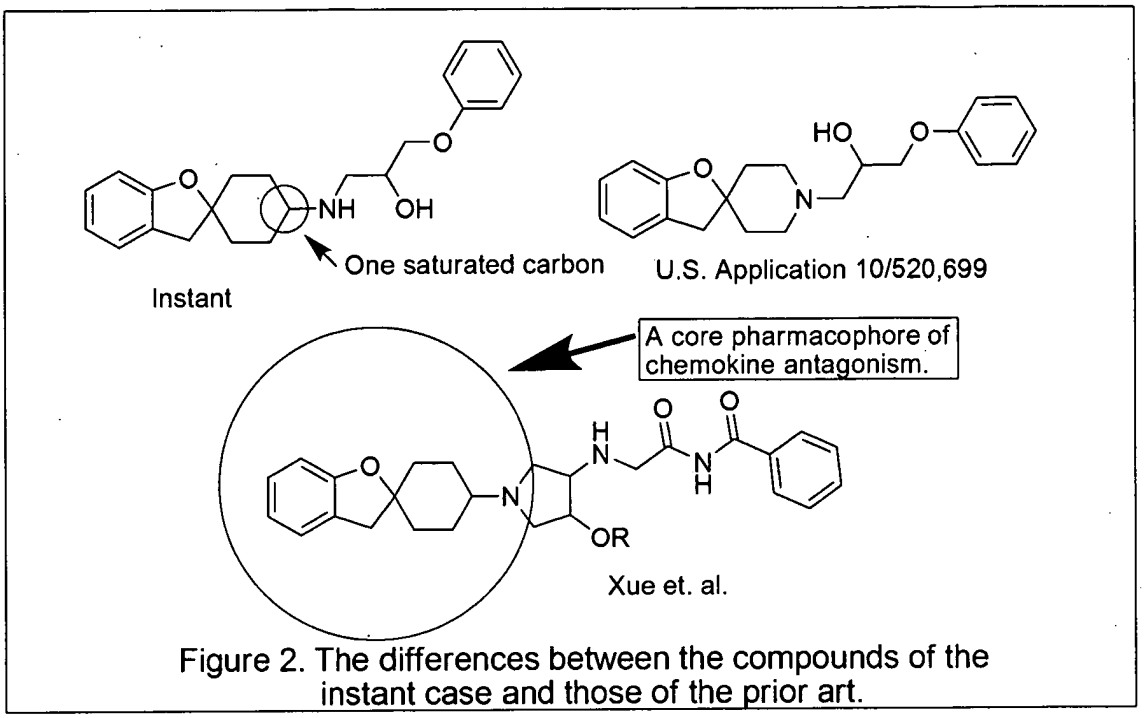


Figure 2. The differences between the compounds of the instant case and those of the prior art.

Finding of prima facie obviousness

Rational and Motivation
(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare the compounds of the instant case. The compounds of the claims at hand are analogs of old compounds. One of ordinary skill would be motivated to make the compounds of the invention because he would expect the compounds to have similar properties, indeed we see that these compounds have the same properties. A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner

concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its **analogs** or isomers, either geometric isomers (*cis* v. *trans*) or position isomers (emphasis added) (*e.g. ortho v. para*)".

This is a provisional obviousness-type double patenting rejection.

6. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 12 of copending Application No. 10/581,171 in view of Xue et. al. U.S. Pre-Grant Publication 2006/0252751. The analysis applied in this action at 5 applies here. This is a provisional obviousness-type double patenting rejection.

7. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 12, 14 of copending Application No. 10/583,468 in view of Xue et. al. U.S. Pre-Grant Publication 2006/0252751. The analysis applied in this action at 5 applies here. Although claim 9 is apparently a claim for "a claim".

8. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9, 13 of copending Application No.

10/520,699 in view of Xue et. al. U.S. Pre-Grant Publication 2006/0252751. The analysis applied in this action at 5 applies here.

This is a provisional obviousness-type double patenting rejection.

9. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory double patenting over claim 1-7, 9, 11 of commonly assigned copending Application No. 11/744,659. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: The copending application is drawn to the same compounds as those of the instant case.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

10. Claims 1-7, 9 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-7, 9, 11 of commonly assigned copending Application No. 11/744,677. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common

subject matter, as follows: The copending application is drawn to the same compounds as those of the instant case.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-6, 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds, does not reasonably provide enablement for the protracted list of compounds bearing the protracted list of substituents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a variety of compounds, bearing multiple substitutions **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic chemist. **(C) The state of the prior art:** Little prior art exists on these complex compounds, however the synthesis will be evaluated on what is known using scientific principles. **(E) The level of predictability in the art:** Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3. As stated in the preface to a recent treatise:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually

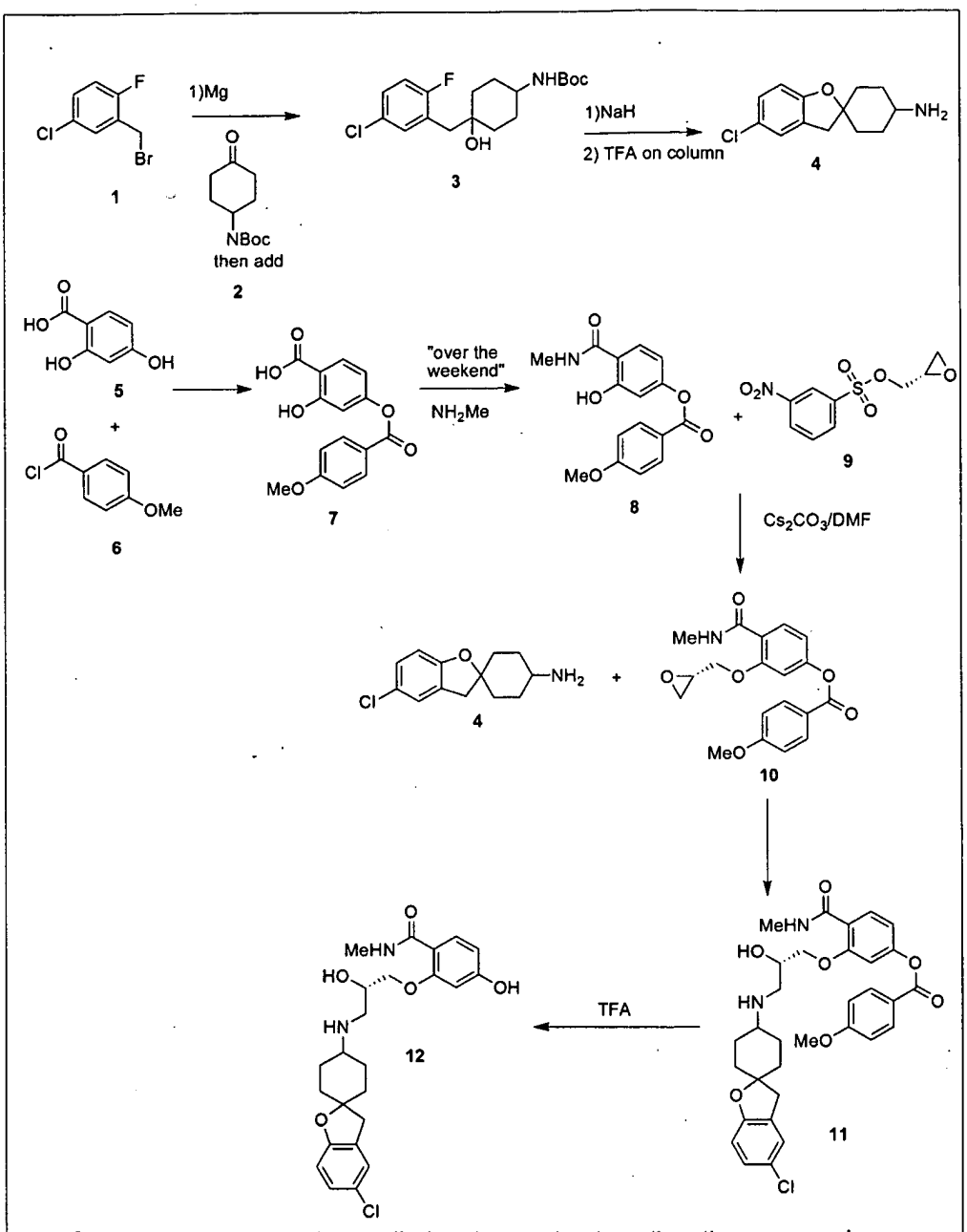
> implies will be able to appraise such work.....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)....." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

(F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention: The examiner will first consider the Markush structure I of claim 1, and discuss the limitations inherent to the paucity of available starting materials, as well as the inherent limitations of the chemistry used to prepare the examples. As per MPEP:

As per MPEP:

> A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in In re Ghiron, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. In re Howarth, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

The synthetic route and starting materials that the applicant has provided to make the scope of this invention has been reproduced below as Scheme1:



Scheme 1. The chemistry relied on to construct applicant's compounds.

The key materials here are the □-bromo-2-fluoro-toluene derivative **1**, the N-Boc-4-amino cylcohexanone **2**, phenols such as **8** bearing amide groups, and glycidols **9**. A search for each of these materials in the Aldrich Chemical Company catalog (St. Louis, MO) was conducted, the reulsts of which are reproduced below:

SIGMA-ALDRICH Home

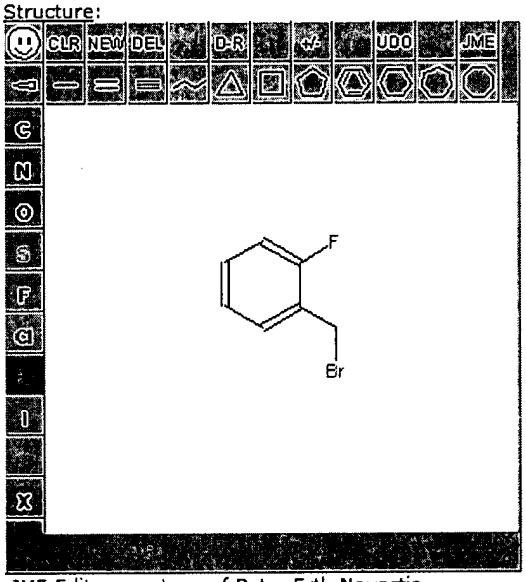
Search |

Enter Search Criteria

Search CLEAR

Search Type: SubStructure (2D)

Structure:



JME Editor courtesy of Peter Ertl, Novartis

SMILES: Load

MW: Between &

Results / Page: 50

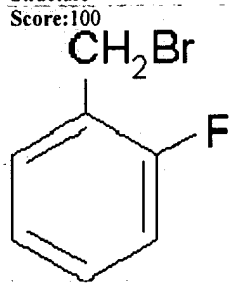
Total Hits: 2000

More Options

Search Results 1-15 of 15 in 0.0 sec. New Search Export

Sort By: MW

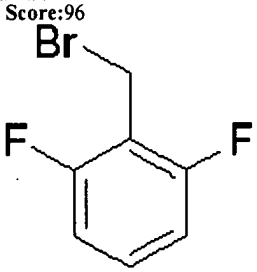
Compound Properties		Structure	Add	Prod. #	Purity
Name:	**2-Fluorobenzyl bromide**	**Score:**100			
IUPAC:	**1-(bromomethyl)-2-fluorobenzene**				
MF:	C_7H_6BrF				
CAS #:	446-48-0				
MW:	189.02			209511	98%
MDL #:	MFCD00000324				
BP:	84 - 85 °C				
FP:	181				
d:	1.5670				



Zoom In

Name: 2,6-Difluorobenzyl bromide
IUPAC: 2-(bromomethyl)-1,3-difluorobenzene
MF: $C_7H_5BrF_2$
CAS #: 85118-00-9
MW: 207.02
MDL #: MFCD00000329
FP: 230

Score:96



Zoom In

83141 purum, ≥95.0% (GC)
264431 97%

Name: 2,5-Difluorobenzyl bromide
IUPAC: 2-(bromomethyl)-1,4-difluorobenzene
MF: $C_7H_5BrF_2$
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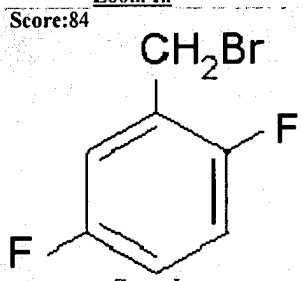
MW: 207.02
MDL #: MFCD00009897
FP: 60
d: 1.6090

Score:84



Zoom In

264423 98%

Name: 2,3-Difluorobenzyl bromide
IUPAC: 1-(bromomethyl)-2,3-difluorobenzene
MF: $C_7H_5BrF_2$
CAS #: 113211-94-2
MW: 207.02
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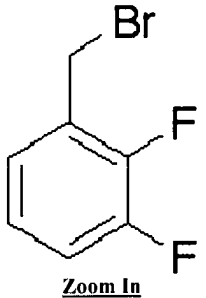
FP: 194
d: 1.6280

Score:86

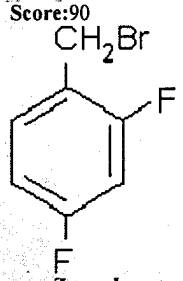


Zoom In

68318 ≥99.5% (GC)
74259 purum, ≥99.5% (GC)
265314 98%

Name: 2,4-Difluorobenzyl bromide
IUPAC: 1-(bromomethyl)-2,4-difluorobenzene
MF: $C_7H_5BrF_2$
CAS #: 23915-07-3
MW: 207.02
MDL #: MFCD00011649
FP: 104
d: 1.6130

Score:90

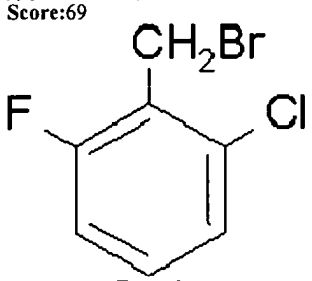


Zoom In

264415 98%

Name: 2-Chloro-6-fluorobenzyl bromide
IUPAC: 2-(bromomethyl)-1-chloro-3-fluorobenzene
MF: C_7H_5BrClF
CAS #: 68220-26-8
MW: 223.47
MDL #: MFCD00040126
FP: 230
d: 1.6290

Score:69



Zoom In

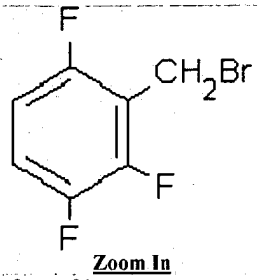
539090 96%

Name: 2,3,6-Trifluorobenzyl bromide
IUPAC: 2-(bromomethyl)-1,3,4-trifluorobenzene
MF: $C_7H_4BrF_3$
CAS #: 151412-02-1

Score:84

449407 97%

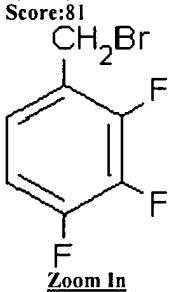
MW:	225.01
MDL #:	MFCD00061208
BP:	114 °C
FP:	195
d:	1.7180



Zoom In

Name:	2,3,4-Trifluorobenzyl bromide
IUPAC:	1-(bromomethyl)-2,3,4-trifluorobenzene
MF:	$C_7H_4BrF_3$
CAS #:	157911-55-2
MW:	225.01
MDL #:	MFCD00061233
FP:	195
d:	1.71

Score:81

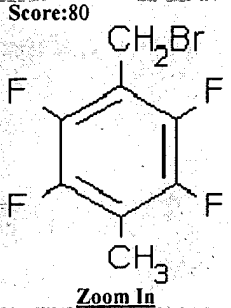


Zoom In

554685 97%

Name:	1-Bromomethyl-4-methyl-2,3,5,6-tetrafluorobenzene
IUPAC:	1-(bromomethyl)-2,3,5,6-tetrafluoro-4-methylbenzene
MF:	$C_8H_5BrF_4$
CAS #:	92814-00-1
MW:	257.02
MDL #:	MFCD03001155
FP:	199

Score:80

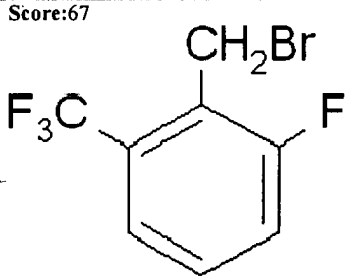


Zoom In

556491 97%

Name:	2-Fluoro-6-(trifluoromethyl)benzyl bromide
IUPAC:	2-(bromomethyl)-1-fluoro-3-(trifluoromethyl)benzene
MF:	$C_8H_5BrF_4$
CAS #:	239087-08-2
MW:	257.02
MDL #:	MFCD00082477
FP:	225

Score:67

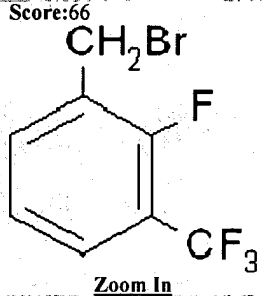


Zoom In

539627 98%

Name:	2-Fluoro-3-(trifluoromethyl)benzyl bromide
IUPAC:	1-(bromomethyl)-2-fluoro-3-(trifluoromethyl)benzene
MF:	$C_8H_5BrF_4$
CAS #:	184970-25-0
MW:	257.02
MDL #:	MFCD00061172

Score:66



Zoom In

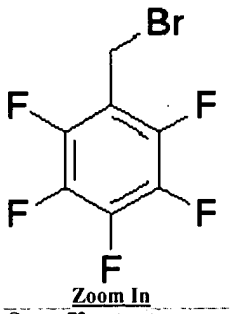
538094 97%

Name:	2,3,4,5,6-Pentafluorobenzyl bromide
IUPAC:	1-(bromomethyl)-2,3,4,5,6-pentafluorobenzene
MF:	$C_7H_2BrF_5$
CAS #:	1765-40-8
MW:	260.99
MDL #:	MFCD00000299
BP:	174 - 175 °C

Score:81

17910 puriss., ≥99.0% (GC)
101052 99%
33001 ampule of 5 g

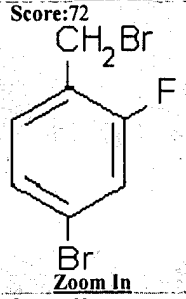
FP:	181
d:	1.7280



Zoom In

Name:	4-Bromo-2-fluorobenzyl bromide
IUPAC:	4-bromo-1-(bromomethyl)-2-fluorobenzene
MF:	$C_7H_5Br_2F$
CAS #:	76283-09-5
MW:	267.92
MDL #:	MFCD00055467

Score:72

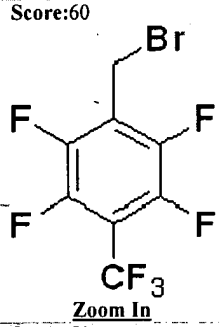


Zoom In

477559 98%

Name:	2,3,5,6-Tetrafluoro-4-(trifluoromethyl)benzyl bromide
IUPAC:	1-(bromomethyl)-2,3,5,6-tetrafluoro-4-(trifluoromethyl)benzene
MF:	$C_8H_2BrF_7$
CAS #:	76437-40-6
MW:	310.99
MDL #:	MFCD00191855
FP:	210
d:	1.8640

Score:60

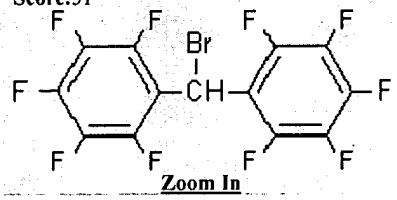


Zoom In

87285 purum, ≥97.0% (GC)
406406 98%

Name:	DECAFLUOROBENZHYDRYL BROMIDE
IUPAC:	DECAFLUOROBENZHYDRYL BROMIDE
MF:	$C_{13}HBrF_{10}$
CAS #:	5736-4-9--2
MW:	427.04
MDL #:	MFCD00017901

Score:51



Zoom In

Most disturbingly we do not find the 5-chloro derivative which is required to synthesize all of the compounds that were actually made. We can see that R_1 can be nothing but fluoro, trifluormethyl or chloro.

Search |

Enter Search Criteria <- Hide Criteria

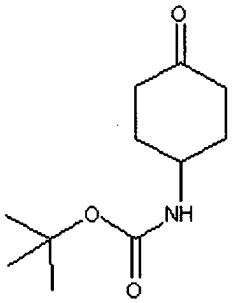
Search | Search on results | CLEAR

Search Type: SubStructure (2D)

Structure:

CLR NEW DEL D-R UDO JME

C N O S F Cl Br I X



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SMILES: Load

MW: Between &

Results / Page: 50

Total Hits: 100

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Search Results 0-0 of 0 in 1.0 sec. New Search

Sort By: MW

Compound Properties Structure Add

No such cyclohexanones appear to be commercially available. While many phenols such as **8** are commercial, it would appear that the amide functionality (reverse as well) is required for activity, based on the fact that applicant has no examples of compounds that are not amides (in the ortho position) and the fact that Xue et. al. (supra) require the amide moiety for antagonism. To the examiners knowledge only one nosylglycidol, namely compound **9,** is commercial. Substituents should be limited to lower alkyl.

According to the U.S. Court of Customs and Patent Appeals in *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 101, "[o]rdinarily no problem in this regard arises since the method of preparing almost all starting materials can be set forth in writing if the materials are not already known and available to the workers in the art, and when this is done the specification is enabling to the public". *In re Argoudelis, De Boer, Eble, and Herr* 168 USPQ 99 at 104, "it is essential that there be no question that, *at the time an application for patent is filed,* (emphasis in original) the invention claimed therein is fully capable of being reduced to practice (i.e., that no technological problems, the resolution of which would require more than ordinary skill and reasonable time, remain in order to obtain an operative, useful embodiment)." That is not the situation here. Rather we find no direction as to how the many required staring materials of formula **1**, **2**, **8,** and **9** are to be obtained. Where may the directions to prepare or buy them be found?

In re Howarth, 210 USPQ 689, (claimed derivatives of clavulanic acid not enabled by specification lacking information of how prepare the clavulanic acid or directions to reference

materials containing such information), *Ex parte Schwarze* 151 USPQ 426 (where starting material is not known to art as of date of filing application, there must be included a description of preparation thereof to enable one skilled in this art to carry out applicant's invention), *Ex parte Moersch* 104 USPQ 122 (claims to process for the production of (1)-yl-p-nitrophenyl-2-dichloracetamindo-propane-1,3-diol not enabled because of failure to describe source or method of obtaining starting compound; although starting compound is identified by means of appropriate name and by structural formula). Genetech Inc Vs Nova Nordisk 42 USPQ 2d 1001 "A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

For guidelines on the relationship of working examples and the size of claimed genus see the MPEP 2164:

WORKING EXAMPLES AND A CLAIMED GENUS For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

2164.03 Relationship of Predictability of the Art and the Enablement Requirement

[R-2] The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839,166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a 'specific and useful teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the

bargain struck by the patent system is a full enabling disclosure of the claimed technology." (citations omitted)).< The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971), stated:

> [I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. [Footnote omitted.]

The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730,734, 169 USPQ 298, 301 (CCPA 1971). However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *Inre Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir.1991). This is because it is not obvious from the disclosure of one species, what other species will work.

If such starting materials could be obtained compounds could be obtained it is very

clear that the protracted list of substituents for R^1 cannot undergo the synthetic procedures given. Nitriles and other electrophiles will also undergo addition by Grignards (Jie Jack Li *Name Reactions A Collection of Detailed Reaction Mechanisms* "Grignard Reaction" Third Expanded Edition Springer 2006, pg. 271-272. Metal halogen exchange between a ("halo") like iodine and a Grignard will also occur (Knochel et. al. *Angew. Chem. Int. Ed.* **2003**, *42*, 4302 –4320). The

"alkylhalo" compounds will undergo metal halogen exchange when in the presence of a Grignard (Knochel ibid.).

Another disturbing feature of what is before the examiner, is the fact that it appears that no assays were performed. These compounds may perform in this assay however this has not been asserted. There is no support in the specification for the use of these compounds as chemokine antagonists. While applicant states on pg. 40 "Compounds are evaluated by their ability to depress the chemotactic response to a standard concentration of M1P-1α chemokine." No evidence is given that these compounds actually were shown to have this activity. Given that similar compounds have the activity we can assume they have this activity (supra). The assumption that a chemokine receptor is involved may be incorrect, given that agonism at other GPCRs (δ-opiod receptors for instance), can lead to down regulation of chemokine receptors via heterodimers or higher oligomer complex formation (Chen et. al. *European Journal of Pharmacology* **2004**, *483*, 175-186.). The complete receptor profile of THP-1 cells is not known. Applicant may consider a binding assay as in Carroll et. al. WO 00/014086 cited by applicant ref. AG pg. 34:

> plate counter.
>
> The activities of test compounds are reported in the Table below as IC_{50} values or the inhibitor concentration required for 50% inhibition of specific binding in receptor binding assays using ^{125}I-RANTES or ^{125}MIP-1α as ligand and THP-1 cell membranes. Specific binding is defined as the total binding minus the non-specific binding; non-specific binding is the amount of cpm still detected in the presence of excess unlabeled Rantes or ^{125}MIP-1α.

or Bondinell et. al. WO 01/64213 A1 pg. 23-25 cited by applicant ref. AH

Biological Data:

CCR5 Receptor Binding Assay

CHO cell membranes (0.25×10^6 cell equivalents) derived from CHO cells stably transfected with CCR5 were incubated with 0.3 ^{125}I-RANTES in a 96 well plate for 45 min. at room temperature (final reaction volume 200 ul). The reaction was terminated by filtration and the filters (GF/C) were washed twelve times with a solution of phosphate buffered saline containing 0.1 % bovine serum albumin and 0.05 % NaN_3. The radioactivity bound to filters was measured by liquid scintillation spectrometry. Non-specific binding was determined in the presence of unlabelled RANTES (10 or 30 nM) and averages 30-50% of total binding.

CCR5 Receptor Functional Assay

The cellular functional assay used to assess antagonist activity of compounds was RANTES-induced Ca^{2+} mobilization in RBL 2H3 cells stably expressing the hCCR5 or mCCR5 receptor (RBL 2H3 hCCR5). Agonist activity is determined by Ca^{2+} mobilization in the same cells which is inhibitable by a selective CCR5 antagonist. Cells were grown to 80-100% confluency in T-150 flasks and washed with phosphate-buffered saline. Cells were lifted from the flasks by treating with 3 mL of 1 mM EDTA for 3 min. at room temperature and diluting to 2 X 10^6 cells/mL with Krebs Ringer Henseleit buffer (KRH; 118 mM NaCl, 4.6 mM KCl, 25 mM $NaHCO_3$, 1 mM KH_2PO_4 and 11 mM glucose) containing 5 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% BSA and centrifuged at 200g for 3 min. Cells were resuspended at 2 X 10^6 cells/mL in the same buffer with 2 µM Fura-2AM, and incubated for 35 min. at 37° C. Cells were centrifuged at 200 x g for 3 min. and resuspended in the same buffer without Fura-2AM, then incubated for 15 min. at 37° C to complete the hydrolysis of intracellular Fura-2AM, and then centrifuged as before. Cells (10^6 cells/mL) were resuspended in cold KRH with 5 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% gelatin and maintained on ice until assayed. For antagonist studies, aliquots (2 mL) of cells were prewarmed at 37° C for 5 min. in 3 mL plastic cuvettes and fluorescence measured in a fluorometer (Johnson Foundation Biomedical Group, Philadelphia, PA, USA) with magnetic stirring and temperature maintained at 37° C. Excitation was set at 340 nm and emission set at 510 nm. Various concentrations of antagonists or vehicle were added and fluorescence monitored for ~15 sec to ensure that there was no change in baseline fluorescence, followed by the addition of 33 nM RANTES. Maximal Ca^{2+} attained after 33 nM RANTES stimulation was calculated as described by Grynkiewicz *et al.*, (1985). The percent of maximal RANTES-induced Ca^{2+} was determined for each concentration of antagonist and the IC_{50}, defined as the concentration of test compound that inhibits 50% of the maximal 33 nM RANTES response, obtained from the concentration-response curves (5-7 concentrations of antagonists). Alternatively, this CCR5 receptor functional assay was performed on murine CCR5 (mCCR5) with a RANTES concentration of 2nM.

The compounds of this invention show CCR5 receptor modulator activity having IC_{50} values in the range of 0.0001 to 100 µM. The full structure/activity relationship has not yet been established for the compounds of this invention. However, given the disclosure herein, one of ordinary skill in the art can utilize the present assays in order to determine which compounds of formula (I) are modulators

Conclusion

12. No claims are allowed. This action is FINAL. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Rita Desai can be reached on (571) 272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

RITA DESAI
PRIMARY EXAMINER
12/12/07